UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,291	12/08/2004	Masahiko Okada	262964US0XPCT	5683

22850 7590 05/25/2010

OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTADT, L.L.P.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER	
SCHUBERG, LAURA J	

ART UNIT	PAPER NUMBER
1657	

NOTIFICATION DATE	DELIVERY MODE
05/25/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@oblon.com
oblonpat@oblon.com
jgardner@oblon.com

Office Action Summary	Application No.	Applicant(s)	
	10/516,291	OKADA ET AL.	
	Examiner	Art Unit	
	LAURA SCHUBERG	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-11,13,14,17-24 and 38-40* is/are pending in the application.

4a) Of the above claim(s) *1 and 4-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13,14,17-24,38-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is responsive to papers filed 02/17/2010.

Claims 1, 4-11, 13, 14, 17-24, 38-40 are pending.

No claims were amended or newly canceled. Claim 40 was newly added.

Claims 1, 4-11 were withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 04/23/2007.

Claims 13, 14, 17-24, 38-40 have been considered on their merits.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 13, 14, 17-24, 38-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Okada et al in view of Miyauchi et al (EP 1148142 A1, as cited in the IDS filed 21 January 2005) and Matsui et al (US 6,194,164).

A kit for selective measurement of triglycerides contained in very low density lipoprotein and intermediate density lipoprotein or in very low density lipoprotein in a test sample is claimed comprising two reagents.

New claim 40 is drawn to the kit of claim 13 which is used for selective measurement of triglycerides contained in very low density lipoprotein in the test sample.

Intended use limitations are only given patentable weight in so far as they require the kit to be in a form suitable for that intended use.

Okada et al teach a reagent comprising a reaction promoting agent (i.e., a selective reaction promoter) that can be a surface-active agent such as a polyoxyalkylene or a derivative thereof, including polyoxyethylene alkyl ether and polyoxyethylene alkyl phenyl ether (i.e., polyoxyalkylene straight-chain alkyl ethers). Okada et al teach that the reaction promoting agent interacts with lipoprotein lipase to eliminate triglycerides in lipoproteins other than very low density lipoproteins and intermediate density lipoproteins (i.e., VLDL and IDL) by carrying out a series of reactions which make hydrogen peroxide or reduced coenzyme. Okada et al teach that the enzymes used for decomposition of triglycerides into hydrogen peroxide for measurement include lipoprotein lipase, which gives glycerol, which is then changed to glycerol 3-phosphate by glycerol kinase, that changes into dihydroxyacetone-3-phosphate by glycerol-3-phosphate oxidase, followed by colored assay of the generated hydrogen peroxide. Also, Okada et al teach that glycerol-3-phosphate dehydrogenase can be used in lieu of glycerol-3-phosphate oxidase to produce NADH so that NADH

can be measured (see, for example, Detailed Description section). Okada et al teach a first reagent comprising a reaction promoting agent and enzymes including lipoprotein lipase as well as other enzymes to produce either hydrogen peroxide or a reduced coenzyme, which eliminates the triglycerides from the lipoproteins other than the VLDL's and the IDL's, which includes those from LDL's and HDL's. Okada et al also teach a second reagent which then quantifies the triglycerides in the VLDL's and the IDL's, comprising a reaction promoting agent and enzymes (i.e., lipoprotein lipase) which can react with the triglycerides to generate either hydrogen peroxide or a reduced coenzyme, wherein the reaction promoting agent can be a polyoxyalkylene or a derivative thereof, including polyoxyethylene alkyl ether and polyoxyethylene alkyl phenyl ether. Furthermore, Okada et al teach that the reagents may also contain reaction "auxiliary substances" (i.e., reaction assistants) which can assist the reaction promoter agents, examples of which include polyanion, halogen ion, and metal ions (see, for example, Detailed Description section). Addition of auxiliary substances for the promotion of selectivity is also taught to be desirable as well (pages 5-6).

While Okada et al do not specifically package the claimed reagents into a kit with the claimed ratio of polyoxyalkylene in its ether or ester compound, use of a kit containing reagents is suggested as acceptable (page 36).

Miyauchi et al beneficially teach reagents for quantitating triglycerides (TG) in lipoproteins, providing a reagent for allowing the reaction of lipoproteins other than the particular lipoprotein, as well as providing lipoprotein lipase (LPL), glycerol kinase (GK), glycerol-3-phosphate oxidase (GPO), and peroxidase. Miyauchi et al suggest that these

reagents are suitable for quantitative analysis (page 3 paragraphs 20-21) and include the form of a kit in which the reagents are divided into two or more parts depending on their components (page 3 paragraph 22). Furthermore, Miyauchi et al beneficially teach that it is useful to add a surfactant or to add an enzyme while allows reaction of a particular lipoprotein (see, for example, page 3 and page 4). Miyauchi et al beneficially teach that in measuring TG in particular lipoproteins, it is preferable to add a reagent for eliminating the reaction of lipoproteins other than the lipoprotein of interest, such as a surfactant which would allows LPL to react specifically with particular lipoproteins, so that a precise measurement of TG in a particular lipoprotein of interest can be made. Subsequently, Miyauchi et al teach that the same sample can then have a second reagent added to it which contains a surfactant that allows reaction of the particular lipoprotein of interest as well as LPL, so as to obtain a measurement of TG in the lipoprotein of interest.

Matsui et al beneficially teach that preferred surfactants which act on lipoproteins other than LDL include polyoxyalkylene oxide derivatives having HLB (i.e., hydrophilic-lipophilic balance) values of not less than 13 and not more than 15. Matsui et al teach that one particular example is polyoxyethylene nonylphenyl ether (see, for example, col. 3, line 35). Matsui et al further teach that surfactants which act on all lipoproteins include polyoxyalkylene oxide derivatives having HLB values of not less than 11 and not more than 13, particularly polyoxyethylene nonylphenyl ether, for example (see, for example, col. 4, lines 10-40). Matsui et al beneficially teach that the method for calculating HLB of surfactants is well-known in the art, a method which is based in part

upon the molecular weight of the hydrophilic portion of the surfactant (e.g., polyoxyethylene). Different concentration ranges for surfactants are taught for the first step (column 3 lines 53-55) and the second step (column 5 lines 18-20) of the quantitating method and these ranges would allow for a ratio of surfactants that would include 1.1 or 1.2 as claimed by Applicant.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the reagent mixtures disclosed by Okada et al based upon the beneficial teachings provided by Miyauchi et al, with respect to the art-recognized method for using a two-step process using different reagents containing surfactants and LPL to determine TG in lipoproteins, and by Matsui et al, with respect to the art-recognized method of using surfactants of a particular HLB value or molecular weight to solubilize specific lipoproteins, as discussed above. Okada et al specifically teach reagents which act on lipoproteins using surfactants that are derivatives of polyoxyalkylene and lipoprotein lipase so as to generate either hydrogen peroxide or reduced coenzyme to determine the amount of triglyceride in VLDL and IDL.

Furthermore, Matsui et al particularly point out that polyoxyethylene nonylphenyl ether is one specific polyoxyalkylene derivative that is a preferred surfactant for acting on lipoproteins, and that the HLB value of a surfactant is important in determining its specificity toward lipoproteins. Matsui et al further beneficially teach that particular HLB values of surfactant are beneficial for acting on particular lipoproteins, and that calculating HLB values is well known in the art, and therefore, it would have been both obvious and beneficial for one of skill in the art at the time the claimed invention was

made to use particular surfactants, as described by both Okada et al and Matsui et al, in particular mole number ratios of the polyoxyalkylene derivatives (i.e., the hydrophilic group) so as to vary the selectivity of the surfactant for different lipoproteins based upon the HBL value, as beneficially taught by Matsui et al. The result-effective adjustment of particular conventional working conditions (e.g., using a particular surfactant and/or using a particular ratio of added polyoxyalkylene in each of the selective reaction promoters) is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan. Clearly all of the claimed ingredients are known in the art to be suitable for use together in methods for quantitating triglycerides in lipoproteins and would thus be obvious for one of ordinary skill in the art to package them as kits. It is well-known in the art to separately package ingredients to be combined together for the known advantage of improved storage and prevention of premature reaction.

In addition, as far as the inclusion of written instructions in the kit, M.P.E.P. § 2112.01 recites, "Where the only difference between a prior art product and a claimed product is printed matter that is not functionally related to the product, the content of the printed matter will not distinguish the claimed product from the prior art." See *In re Ngai* and *In re Gulack* (citations omitted).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole, was *prima facie* obvious to one of

ordinary skill in the art at the time the claimed invention was made, as evidenced by the cited references, especially in the absence of evidence to the contrary.

Response to Arguments

Applicant's arguments filed 02/17/2010 have been fully considered but they are not persuasive.

Applicant argues that the combination of the references does not describe or suggest a kit and a method for selective measurements of triglycerides contained in the very low density lipoprotein and intermediate density lipoprotein (as in claims 1 and 13) or very low density lipoprotein (as in claim 40). Applicant asserts that the primary feature of the claimed kit and method is to use the two lipoprotein lipases having different properties, wherein the activity of the lipoprotein lipase contained in the first reagent depends on the concentration of a surfactant, while that of the lipoprotein lipase contained in the second reagent hardly depends on the concentration of a surfactant. Applicant's arguments and evidence of unexpected results are all drawn to the method of using the kit.

This is not found persuasive because the claims under examination are the kit claims not the method claims. The intended use limitations of the kit claims are only given patentable weight in so far as they require that the kit be in a form suitable for the intended use. Unexpected results with regard to the method of using the kit are not persuasive in this case. Unexpected results with regard to the kit itself and the manner

in which the reagents are presented in the kit would be required to overcome the obviousness rejections.

In submitting evidence asserted to establish unobvious results, there is a burden on an applicant to indicate how the examples asserted to represent the claimed invention are considered to relate to the examples intended to represent the prior art and, particularly, to indicate how those latter examples do represent the closest prior art. See *In re Borkowski,* 595 F.2d 713, 184 USPQ 29 (CCPA 1974); *In re Goodman,* 339 F.2d 228, 144 USPQ 30 (CCPA 1964).

The evidence relied upon should also be reasonably commensurate in scope with the subject matter claimed and illustrate the claimed subject matter "as a class" relative to the prior art subject matter "as a class." *In re Susi,* 440 F.2d 442, 169 USPQ 423 (CCPA 1971); *In re Hostettler,* 429 F.2d 464, 166 USPQ 558 (CCPA 1970). See, also, *In re Lindner,* 457 F.2d 506, 173 USPQ 356 (CCPA 1972).

It should also be established that the differences in the results are in fact unexpected and unobvious and of both statistical and practical significance. *In re Merck,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); *In re Longi,* 759 F. 2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Klosak,* 455 F2d 1077, 173 UAPQ 14 (CCPA 1972); *In re D'Ancicco,* 429 F.2d 1244, 169 USPQ 303 (CCPA 1971). *Ex parte Gelles,* 22 USPQ2d 1318 (BPAI 1992).

Therefore since the claims examined are kit claims, the evidence of unexpected results has to be commensurate in scope with these claims and demonstrate how it would be unexpected to combine the reagents in the manner as Applicant has claimed.

However, it appears from Applicant's statements that the invention lies in the method of using the kit rather than the kit itself.

Applicant argues that the combination of the Okada et al, Miyauchi et al and Matsui et al do not describe or suggest using different lipases having different activities in two different reagents and selecting a specific molar ratio of the selective reagents. Applicant points to specific working examples in the references to demonstrate that the inclusion of 2 different lipases are not taught by the references.

This is not found persuasive because the teachings of the references are not limited to the working examples that they provide. Okada et al specifically teaches that one of ordinary skill in the art may make an alternative reaction promoting agent by combining two or more kinds of ingredients and suggests modifying the concentrations, content and specifically the enzymes used (page 35 of the translation). Clearly Okada et al suggest that these ingredients may be used in different combinations and separated into two reagents for use in the method.

Applicant argues that Matsui et al do not teach adjusting HLB values so as surfactants act on different lipoproteins and different lipoprotein lipases, or adjusting a ratio of the average moles of polyoxyalkylene in its ether or ester compound. Applicant asserts that the HLB value reflects a degree to which a surfactant is hydrophilic or

lipophilic and does not show how many moles of a surfactant is added or ratio of surfactants in two steps.

This is not found persuasive because Matsui et al teach that the method for calculating HLB of surfactants is well-known in the art, a method which is based in part upon the molecular weight of the hydrophilic portion of the surfactant (e.g., polyoxyethylene). Also, different concentration ranges for surfactants are taught for the first step (column 3 lines 53-55) and the second step (column 5 lines 18-20) of the quantitating method and these ranges would allow for a ratio of surfactants that would include 1.1 or 1.2 as claimed by Applicant. Clearly the use of surfactants in the same ratio as claimed by Applicant is known in the art.

Applicant argues that the methods and reagents of Okada et al, Miyauchi et al and Matsui et al are different from each other because they use different enzymes, measure different substances and exhibit different behaviors towards surfactants such as polyalkylene derivatives. Applicant asserts that it would not have been obvious what surfactants and HLB values to select based on the contradictory data of Okada et al and Matsui et al for the selective measurement of TG in VLDL and IDL.

This is not found persuasive as the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Okada et al specifically teach reagents which act on lipoproteins using surfactants that are derivatives of polyoxyalkylene and lipoprotein lipase so as to generate either hydrogen peroxide or reduced coenzyme to determine the amount of triglyceride in VLDL and IDL. Furthermore, Matsui et al particularly point out that polyoxyethylene nonylphenyl ether is one specific polyoxyalkylene derivative that is a preferred surfactant for acting on lipoproteins, and that the HLB value of a surfactant is important in determining its specificity toward lipoproteins. Clearly one of ordinary skill in the art would be motivated to select an ether or ester compound of a polyoxyalkylene for use in the method of Okada et al based on these teachings. Clearly the reagents that Applicant is claiming for packaging in a kit are well known in the art of measuring triglycerides with selectivity and claimed ratio of the surfactants does not appear to be outside the range suggested by the prior art as well and therefore the prior art renders obvious Applicant's invention as claimed.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA SCHUBERG whose telephone number is (571)272-3347. The examiner can normally be reached on Mon-Fri 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leon B Lankford/
Primary Examiner, Art Unit 1651

Laura Schuberg